Original Article

Cukurova Anestezi ve Cerrahi Bilimler Dergisi

Diagnostic and Economic Impact of Colposcopy versus Dual Stain Triage in Women with Non-16/18 hrHPV Positive and NILM Cytology

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Abstract

Objective: To evaluate the diagnostic yield and cost-effectiveness of immediate colposcopy versus p16/Ki-67 dual stain (DS) triage in women with non-16/18 high-risk HPV (hrHPV) positivity and normal cervical cytology (NILM) in a tertiary care setting in Türkiye. **Materials and Methods:** This retrospective cohort study included 454 unvaccinated women with non-16/18 hrHPV positivity and NILM cytology between December 2023 and May 2025. All underwent colposcopy with biopsy when indicated. A decision tree model compared two strategies: (1) immediate colposcopy for all, and (2) DS triage with colposcopy limited to DS-positive cases. DS performance metrics (sensitivity: 70.7%, specificity: 70.8%) were derived from literature. Total costs, colposcopy numbers, CIN2+ detection, and missed cases were calculated. **Results:** Among 454 patients, 10 (2.2%) were diagnosed with CIN2+ (7 CIN2, 3 CIN3). Immediate colposcopy detected all cases at a total cost of $7,491 with 454 procedures. The DS triage strategy required only 136 colposcopies (70% reduction) but missed 3 CIN2+ lesions and cost $24,944—a 233% increase. **Conclusion:** While DS triage reduced the number of colposcopies, it missed 30% of CIN2+ lesions and significantly increased costs. In under-screened, high-risk populations such as in Türkiye, immediate colposcopy remains a more effective and economically viable strategy for managing non-16/18 hrHPV-positive, NILM patients.

Keywords: Colposcopy; Human papillomavirus infections; Uterine cervical neoplasms; Cost-benefit analysis; Dual stain

Received:
15.02.2026
Accepted:
09.06.2026
Published:
30.06.2026

1. Introduction

Cervical cancer is the eighth most common cancer among women in Türkiye, with an incidence rate of 4.7 per 100,000 in 2025[1,2]. Persistent human papillomavirus (HPV) infection is responsible for cervical cancer development[3,4]. Screening strategies that utilize HPV testing either as a standalone method or in conjunction with cytology have demonstrated superior sensitivity compared to cytology alone in identifying high-grade squamous intraepithelial lesions (HSIL)[5]. However, despite its high sensitivity, HPV DNA testing is limited by a relatively low positive predictive value, as the majority of hrHPV

infections resolve spontaneously[6]. As a result, additional triage methods are essential to reduce unnecessary follow-up procedures[7].

Among the biomarkers investigated for triage purposes, p16/Ki-67 dual staining (DS) has gained substantial attention. P16INK4a is a tumor suppressor protein involved in cell-cycle regulation, whereas Ki-67 is a well-established marker of active cellular proliferation[8]. The positivity rate of p16/Ki-67 dual staining has been shown to increase significantly with higher cytological and/or histological severity of cervical lesions[9]. Although women who are NILM in cytology but positive for hrHPV types other than HPV 16 and 18 still remain at increased risk of developing HSIL[10].

In women testing positive for hrHPV genotypes other than 16 or 18 and presenting with normal cytology, according to the 2019 ASCCP guidelines, the recommended management consists of repeat HPV testing combined with cytology after one year[11,12]. According to recent guideline updates, DS positivity warrants immediate colposcopic assessment, whereas a negative result supports extending surveillance with repeat HPV testing after 12 months[13,14].

Türkiye has implemented a nationwide cervical cancer screening program centered on HPV DNA and reflex cytology testing, targeting women aged 30–65 with a five-year screening interval. DS testing is not available for cytology assessment in Türkiye[15]. The present study aims to investigate whether immediate colposcopy is justified in this subgroup and to assess the cost-effectiveness of incorporating DS testing into the diagnostic pathway in a tertiary care hospital in Türkiye.

2. Materials and Methods

This retrospective study was conducted at the Gynecologic Oncology Surgery Clinic of İzmir City Hospital, following approval by the institutional ethics committee (decision date: 24/12/2025; decision number: 2025/653). A total of 3,097 patients underwent colposcopic examination between 25 December 2023 and 1 November 2025. Among these, 454 patients tested positive for hrHPV types other than HPV 16 and 18 with NILM cytology; 126 biopsies were obtained from indicated cases. Patients with inadequate biopsy samples, pregnancy, HPV 16/18 positivity, prior history of HPV positivity, or a history of HPV vaccination were excluded.

2.1.Liquid-Based Cytology

ThinPrep™ (Hologic, Inc., Bedford, MA, USA) liquid-based cytology (LBC) was used. All samples were evaluated by experienced pathologists according to the 2014 Bethesda System terminology.

2.2.HPV Testing

HPV genotyping was performed using the Roche Cobas 4800 system (Roche Molecular Systems, Pleasanton, CA, USA). This assay separately identifies HPV 16 and HPV 18, while simultaneously detecting 12 other high-risk HPV genotypes (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), collectively categorized as non-16/18 hrHPV types.

2.3.Colposcopic Examination

All colposcopic procedures were conducted by an experienced gynecologist using standard technique. A 5% acetic acid solution was applied to identify acetowhite changes. When indicated, multiple targeted cervical biopsies and/or endocervical curettage were obtained and submitted for histopathologic evaluation.

2.4.Economic Analysis

A simplified cost analysis compared two management strategies: (1) immediate colposcopic evaluation for all patients, and (2) DS triage with colposcopy reserved for DS-positive cases. DS performance parameters (sensitivity: 70.7%, specificity: 70.8%) were

derived from Wentzensen et al[16]. Unit costs were set at $16.5 USD per colposcopy and $50 USD per DS test, reflecting approximate procedural costs in a Turkish tertiary public hospital[17]. True positives, false negatives, true negatives, and false positives were estimated using a diagnostic decision tree. Total costs, colposcopy numbers, CIN2+ detection, and missed cases were computed for both strategies.

2.5.Statistical Analysis

All statistical analyses were carried out using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± SD, while categorical variables were summarized as frequencies and percentages.

3. Results

During the study period, 3,097 women underwent colposcopic evaluation. Of these, 454 patients (14.6%) had non-16/18 hrHPV positivity with NILM cytology. Among 142 patients with biopsy results, the mean age was 42.0 ± 11.7 years (range 22–69). Ninety-three (65.5%) were premenopausal and 49 (34.5%) postmenopausal. One hundred and ten patients (77.5%) were smokers. Histopathological evaluation revealed normal histology in 89 patients (62.6%), CIN1 in 43 (30.2%), CIN2 in 7 (4.9%), and CIN3 in 3 (2.1%). Demographic and clinical characteristics are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the study population

Characteristic	n (%)
Total number of patients	142
Mean age (years)	42.0 ± 11.7
Median age – Min–Max (years)	42 (22–69)
Premenopausal patients	93 (65.5%)
Postmenopausal patients	49 (34.5%)
Smoker	110 (77.5%)
Non-smoker	32 (22.5%)
Normal histology	89 (62.6%)
CIN 1	43 (30.2%)
CIN 2	7 (4.9%)
CIN 3	3 (2.1%)

Cost analysis results are shown in Table 2. Immediate colposcopy for all 454 patients incurred a total diagnostic cost of $7,491 USD. The DS-based selective colposcopy strategy would result in 136 colposcopic procedures (70% reduction), avoiding 318 unnecessary colposcopies, but would miss 3 CIN2+ cases (detecting only 7 of 10). The total cost for the DS-based strategy was $24,944 USD—$17,453 more than immediate colposcopy, representing a 233% cost increase despite a 70% reduction in colposcopies.

Table 2. Cost analysis summary: immediate colposcopy versus dual stain triage

Parameter	Immediate Colposcopy	DS + Selective Colposcopy
Total number of patients	454	454
CIN2+ cases	10	10
Colposcopies performed	454	136
Colposcopies avoided	0	318
DS tests performed	0	454
CIN2+ cases detected	10	7
CIN2+ cases missed	0	3
Total cost (USD)	$7,491	$24,944

DS: Dual stain; CIN: Cervical Intraepithelial Neoplasia.

4. Discussion

In this retrospective cohort study, we investigated the clinical outcomes and cost-effectiveness of immediate colposcopy versus DS-based triage in women with non-16/18 hrHPV and NILM cytology. Our analysis revealed that 7% (10/142) of these women were diagnosed with CIN2+ lesions upon colposcopic biopsy. When compared with previously published studies, our study demonstrated a similar prevalence. Aydın et al. and Najib et al. documented rates of 8.3% and 4.1%, respectively[18,19]. In large-scale studies, Kabaca et al. found CIN2+ in 6.4% and Koyuncu et al. reported HSIL in 6.2% of a general screening cohort[20,21].

In countries like Türkiye, where HPV vaccination has not yet been integrated into the national immunization program and participation in organized screening remains suboptimal, the risk profile of the screened population is notably different from countries with higher prevention coverage. Our selected cohort consisted exclusively of unvaccinated women with a high prevalence of smoking (77.5%) and limited engagement with longitudinal follow-up protocols. These cumulative risk factors elevate the baseline probability of detecting clinically significant disease. Therefore, relying solely on repeat testing at 12-month intervals may not be suitable in such settings[25].

Based on a sensitivity of 70.7% derived from literature data, the DS triage approach was associated with a 70% reduction in colposcopies but would have failed to detect approximately 30% of CIN2+ cases. Additionally, our cost analysis demonstrated that the DS-based strategy incurred a 233% increase in overall expenditure compared to universal colposcopy, primarily due to the higher unit cost of DS testing. These findings underscore the need for immediate colposcopy in selected high-risk groups, especially where screening coverage and patient compliance are limited[16].

Unlike studies conducted in Thailand and the United States which were based on large-scale population data and incorporated well-established CIN prevalence and cervical cancer incidence rates[26,27], our analysis relies on local cohort data due to the absence of a nationwide registry on the prevalence of cervical dysplasia and invasive cancer. These findings underscore the need for national prevalence studies and health economic evaluations to better inform cervical cancer prevention policies.

Study Limitations

This study has several limitations. The retrospective design may introduce selection and information bias. The sample size for post-treatment HPV follow-up was limited, and the single tertiary care center setting may limit generalizability. The lack of long-term follow-up prevents assessment of recurrence rates or long-term HPV persistence. Future prospective studies with larger cohorts and extended follow-up durations are warranted.

5. Conclusion

While DS triage can effectively reduce unnecessary colposcopies, its lower sensitivity may compromise detection of high-grade lesions in non-16/18 hrHPV-positive NILM patients. In high-prevalence settings or tertiary care centers where the threshold for diagnostic intervention is lower, immediate colposcopy remains a more cost-effective and clinically prudent strategy.

Author Contributions: All authors contributed equally to the conception, design, data collection, analysis, interpretation, and preparation of the manuscript. All authors have read and approved the final version.

Ethical Approval: This study was approved by the Institutional Ethics Committee of İzmir City Hospital (Decision date: 24/12/2025; Decision No: 2025/653). The study was conducted in accordance with the Declaration of Helsinki.

Conflict of Interest: The authors declare no conflicts of interest.

Funding: This study received no external funding.

Data Availability: The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons but are available from the corresponding author on reasonable request.

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